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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/787,421	02/26/2004	Majed M. Hamawy	960296.99187	5432

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EXAMINER	
ROONEY, NORA MAUREEN	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
12/03/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

pat-dept@quarles.com

Office Action Summary	Application No.	Applicant(s)	
	10/787,421	HAMAWY, MAJED M.	
	Examiner	Art Unit	
	Nora M. Rooney	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,9 and 14-17* is/are pending in the application.

4a) Of the above claim(s) *14-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 9 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed on 09/20/2007 is acknowledged.

2. Claims 2, 9 and 14-17 are pending.

4. Claims 14-16 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/02/2006.

5. Claims 2, 9 and 17 are currently under examination as they read on a method for monitoring whether an animal is experiencing kidney transplant rejection by detecting the protein of SEQ ID NO:1 in a kidney tissue sample.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 2, 9 and 17 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention for the same reasons as set forth in the Office Action mailed on 08/13/2007.

Applicant's arguments filed on 09/20/2007 have been fully considered, but are not found persuasive.

Applicant argues:

"It was noted by the undersigned that:

(a) the homogenation process would fragment the marker protein (and thus the claims did cover what was regarded as the invention);

(b) the antiphosphotyrosine antibody could detect the phosphorylated versions, and in any event the application taught how to make monoclonal and polyclonal antibodies which would do so as well;

(c) there was no omitted step as the claims did recite contacting, detection and evaluation steps, and in any event methods for contacting the phosphorylated versions were in the claims;

(d) the specification did enable and describe, as well, antibodies to bind to the marker protein or its fragments;

(e) the specification did describe relevant size parameters for the gel visualization technique.

After discussing these points examiner Haddad noted that the only remaining PTO concern related to the desire for a confirmation that the antiphosphotyrosine antibody would not be picking up unrelated fragments in such quantities that would create a high risk of false negatives. While Applicant pointed out that the monoclonal/polyclonal disclosure in the original specification would in any event resolve that concern, examiner Haddad noted that the concern could be addressed by Applicant submitting a declaration confirming that such "noise" has not been a problem given the perceived specificity under test conditions.

The enclosed declaration confirms that under the taught conditions only the relevant fragment shows up in any meaningful quantity in the size range. Further, it confirms that even if one overexposed the visualization process the contrast between a healthy patient marking and the type of background clutter caused by the overexposure, still would typically leave one skilled in the art able to easily determine whether the

healthy patient marking is still present in essentially the expected healthy patient amounts."

Applicant also submitted a declaration executed by Majed M. Hamawy on 09/17/2007 that argues:

"1. I am the named inventor of the above described patent application.

2. I am very familiar with the visualization techniques, and the results thereof, as described in the above application in which homogenates of kidneys from animals were subjected to size cutoff filters, with selected size ranges being subjected to gel electrophoresis followed by immunoblotting with an antiphosphotyrosine antibody.

3. I believe that one of ordinary skill in the art, using the description of these techniques contained in the above application, would be able to readily detect, with reasonable specificity, the extent to which the antiphosphotyrosine antibody had bound to an SBP-1/marker based peptide within the specified size range where the peptide has a phosphorylated tyrosine.

4. In this regard, in some of my experiments no peptides having phosphorylated tyrosine showed up in the selected size range (indicating kidney rejection). In others a phosphorylated tyrosine containing peptide based on SBP-1 did show up in the selected size range.

5. I am not aware of any experiments of this type where a phosphorylated tyrosine containing peptide from other than the marker protein turned up in the size range in sufficient prominence to cause a false negative problem. Of course, by overexposing beyond normal exposure times one can perceive very minor amounts of background "noise" within the size range. However, this is in such small amounts that even under overexposure conditions that noise has always been readily distinguishable from the prominence of an SBP-I based peptide within the size range that we regularly see in the case of healthy animal testing.

6. In any event, as noted in the above application, and as is evident from our laboratory's article Jose R. Torrealba et al., 5 Amer. Journal of Transplantation 58-67 (2005) (using an antibody to SBP-I rather than antiphosphotyrosine antibody), I believe that using the teachings of my application, one of ordinary skill in the art could readily develop antibodies having great specificity from the marker proteins I have identified and described the sequence of. "

For the same reasons as set forth in the Office Action mailed on 08/13/2007, it is unclear why anti-phosphytyrosine antibody would only detect the SBP-1 protein or fragments in the 20-

80 kD size range. Applicant's arguments and Declaration are insufficient to overcome the instant rejection for many reasons. First, the claims do not recite any steps for size cutoff filtering or antibody labeling times, so those limitations cannot be read into the claims. Further, the Examiner is not persuaded by Applicant's Declaration and argument that after size cutoff filtering only SBP-1 protein and fragments would be detected under "normal" exposure times. The Examiner is supplying three representative evidentiary references amongst the numerous available to show a 20-80 kD protein in kidney cells having phosphorylated tyrosines that can be detected by anti-phosphotyrosine antibodies. Kerr et al. teaches that IκB alpha protein is a 37 kD protein (PTO-892, Reference U; In particular, abstract). Jalal et al. teaches that IκB alpha may be detected by anti-phosphotyrosine antibodies in kidney cells (PTO-892, Reference V; In particular, Figure 3). Wardle et al. teaches that IκB alpha binds to and inhibits the activity of NKκB in kidney cells (PTO-892, Reference W; In particular, whole document). When IκB alpha is phosphorylated, it is tagged by ubiquitin for proteolysis to that NKκB may translocate to the nucleus and act as a transcription factor. Wardle et al. also teaches that NKκB controls a wide variety of biological responses in the kidney. Therefore, the Examiner is not persuaded that other proteins in the 20-80 kD range are not significantly detected by the recited method. IκB alpha is one of many proteins in that size range that are tyrosine phophorylated, ubiquitously or as a part of numerous cellular responses. Therefore, tyrosine phosphorylated SBP-1 is not specifically detected using antibodies to SBP-1 or phosphotyrosine alone.

8. Claims 2, 9 and 17 stand rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps for the same reasons as set forth in the Office Action mailed on 08/13/2007.

Applicant's arguments filed on 09/20/2007 have been fully considered, but are not found persuasive.

Applicant argues:

"It was noted by the undersigned that:

(a) the homogenation process would fragment the marker protein (and thus the claims did cover what was regarded as the invention);

(b) the antiphosphotyrosine antibody could detect the phosphorylated versions, and in any event the application taught how to make monoclonal and polyclonal antibodies which would do so as well;

(c) there was no omitted step as the claims did recite contacting, detection and evaluation steps, and in any event methods for contacting the phosphorylated versions were in the claims;

(d) the specification did enable and describe, as well, antibodies to bind to the marker protein or its fragments;

(e) the specification did describe relevant size parameters for the gel visualization technique.

After discussing these points examiner Haddad noted that the only remaining PTO concern related to the desire for a confirmation that the antiphosphotyrosine antibody would not be picking up unrelated fragments in such quantities that would create a high risk of false negatives. While Applicant pointed out that the monoclonal/polyclonal disclosure in the original specification would in any event resolve that concern, examiner Haddad noted that the concern could be addressed by Applicant submitting a declaration confirming that such "noise" has not been a problem given the perceived specificity under test conditions.

The enclosed declaration confirms that under the taught conditions only the relevant fragment shows up in any meaningful quantity in the size range. Further, it confirms that even if one overexposed the visualization process the contrast between a healthy patient marking and the type of background clutter caused by the overexposure,

still would typically leave one skilled in the art able to easily determine whether the healthy patient marking is still present in essentially the expected healthy patient amounts."

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"1. I am the named inventor of the above described patent application.

2. I am very familiar with the visualization techniques, and the results thereof, as described in the above application in which homogenates of kidneys from animals were subjected to size cutoff filters, with selected size ranges being subjected to gel electrophoresis followed by immunoblotting with an antiphosphotyrosine antibody.

3. I believe that one of ordinary skill in the art, using the description of these techniques contained in the above application, would be able to readily detect, with reasonable specificity, the extent to which the antiphosphotyrosine antibody had bound to an SBP-1/marker based peptide within the specified size range where the peptide has a phosphorylated tyrosine.

4. In this regard, in some of my experiments no peptides having phosphorylated tyrosine showed up in the selected size range (indicating kidney rejection). In others a phosphorylated tyrosine containing peptide based on SBP-1 did show up in the selected size range.

5. I am not aware of any experiments of this type where a phosphorylated tyrosine containing peptide from other than the marker protein turned up in the size range in sufficient prominence to cause a false negative problem. Of course, by overexposing beyond normal exposure times one can perceive very minor amounts of background "noise" within the size range. However, this is in such small amounts that even under overexposure conditions that noise has always been readily distinguishable from the prominence of an SBP-I based peptide within the size range that we regularly see in the case of healthy animal testing.

6. In any event, as noted in the above application, and as is evident from our laboratory's article Jose R. Torrealba et al., 5 Amer. Journal of Transplantation 58-67 (2005) (using an antibody to SBP-I rather than antiphosphotyrosine antibody), I believe that using the teachings of my application, one of ordinary skill in the art could readily develop antibodies having great specificity from the marker proteins I have identified and described the sequence of. "

For the same reasons as set forth in the Office Action mailed on 08/13/2007, it is unclear why anti-phosphytyrosine antibody would only detect the SBP-1 protein or fragments in the 20-80 kD size range. Applicant's arguments and Declaration are insufficient to overcome the instant rejection for many reasons. First, the claims do not recite any steps for size cutoff filtering or antibody labeling times, so those limitations cannot be read into the claims. Further, the Examiner is not persuaded by Applicant's Declaration and argument that after size cutoff filtering only SBP-1 protein and fragments would be detected under "normal" exposure times. The Examiner has supplied three representative evidentiary references *supra* amongst the numerous available to show a 20-80 kD protein in kidney cells having phosphorylated tyrosines that can be detected by anti-phosphotyrosine antibodies. Therefore, the Examiner is not persuaded that other proteins in the 20-80 kD range are not significantly detected by the recited method. IκB alpha is one of many proteins in that size range that are tyrosine phophorylated, ubiquitously or as a part of numerous cellular responses. Tyrosine phosphorylated SBP-1 is not specifically detected using antibodies to SBP-1 or phosphotyrosine alone. Therefore, essential steps are omitted in the recited method of monitoring whether an animal is experiencing kidney transplant rejection.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 2, 9 and 17 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: a method of monitoring whether an animal that has received a transplanted kidney is experiencing kidney transplant rejection, the method comprising: analyzing a sample of the kidney of the animal for the presence of a marker protein selected from the group consisting of: (a) phosphorylated protein which is SEQ:ID NO. 1 in a form comprising phosphorylated tyrosine; and (b) protein which is SEQ: ID NO. 1; wherein the analyzing comprises: contacting the sample or a homogenate thereof with **a labeled antibody that specifically binds to SEQ ID NO:1**; detecting the extent to which labeled antibody becomes bound to the marker protein or said fragment as a result thereof; and either: (i) comparing the amount of marker protein bound to the labeled antibody to a known standard to diagnose whether the animal is experiencing kidney transplant rejection, whereby the method is conducted such that if no such marker protein is thereby detected in the sample, or if the amount of marker protein thereby detected in the sample is below a known standard level, such a result would be indicative of kidney transplant rejection; or (ii) comparing the amount of said fragment bound to the labeled antibody to a known standard to diagnose whether the animal is experiencing kidney transplant rejection, whereby the method is conducted such that if no such fragment bound to the labeled antibody is thereby detected, or if the amount of such fragment bound to the labeled antibody thereby detected is below a known standard level, such a result would be indicative of kidney transplant rejection of claim 17; wherein the animal is a primate of claim 2; and wherein the animal is a human of claim 9; does not reasonably provide **enablement** for: a method of monitoring whether an animal that has received a transplanted kidney is experiencing kidney transplant rejection, the method comprising: analyzing a sample of the

kidney of the animal for the presence of a marker protein selected from the group consisting of: (a) phosphorylated protein which is SEQ:ID NO. 1 in a form comprising phosphorylated tyrosine; and (b) protein which is SEQ: ID NO. 1; wherein the analyzing comprises: contacting the sample or a homogenate thereof with **a labeled antibody capable of binding to the marker protein in the sample, or to a fragment of the marker protein** in the homogenate; detecting the extent to which labeled antibody becomes bound to the marker protein or said fragment as a result thereof; and either: (i) comparing the amount of marker protein bound to the labeled antibody to a known standard to diagnose whether the animal is experiencing kidney transplant rejection, whereby the method is conducted such that if no such marker protein is thereby detected in the sample, or if the amount of marker protein thereby detected in the sample is below a known standard level, such a result would be indicative of kidney transplant rejection; or (ii) comparing the amount of said fragment bound to the labeled antibody to a known standard to diagnose whether the animal is experiencing kidney transplant rejection, whereby the method is conducted such that if no such fragment bound to the labeled antibody is thereby detected, or if the amount of such fragment bound to the labeled antibody thereby detected is below a known standard level, such a result would be indicative of kidney transplant rejection of claim 17; wherein the animal is a primate of claim 2; and wherein the animal is a human of claim 9. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons as set forth in the Office Action mailed on 09/20/2007.

Applicant's arguments filed on 09/20/2007 have been fully considered, but are not found persuasive.

Applicant argues:

"It was noted by the undersigned that:

(a) the homogenation process would fragment the marker protein (and thus the claims did cover what was regarded as the invention);

(b) the antiphosphotyrosine antibody could detect the phosphorylated versions, and in any event the application taught how to make monoclonal and polyclonal antibodies which would do so as well;

(c) there was no omitted step as the claims did recite contacting, detection and evaluation steps, and in any event methods for contacting the phosphorylated versions were in the claims;

(d) the specification did enable and describe, as well, antibodies to bind to the marker protein or its fragments;

(e) the specification did describe relevant size parameters for the gel visualization technique.

After discussing these points examiner Haddad noted that the only remaining PTO concern related to the desire for a confirmation that the antiphosphotyrosine antibody would not be picking up unrelated fragments in such quantities that would create a high risk of false negatives. While Applicant pointed out that the monoclonal/polyclonal disclosure in the original specification would in any event resolve that concern, examiner Haddad noted that the concern could be addressed by Applicant submitting a declaration confirming that such "noise" has not been a problem given the perceived specificity under test conditions.

The enclosed declaration confirms that under the taught conditions only the relevant fragment shows up in any meaningful quantity in the size range. Further, it confirms that even if one overexposed the visualization process the contrast between a healthy patient marking and the type of background clutter caused by the overexposure, still would typically leave one skilled in the art able to easily determine whether the healthy patient marking is still present in essentially the expected healthy patient amounts."

Applicant also submitted a declaration executed by Majed M. Hamawy on 09/17/2007 that argues:

"1. I am the named inventor of the above described patent application.

2. I am very familiar with the visualization techniques, and the results thereof, as described in the above application in which homogenates of kidneys from animals were

subjected to size cutoff filters, with selected size ranges being subjected to gel electrophoresis followed by immunoblotting with an antiphosphotyrosine antibody.

3. I believe that one of ordinary skill in the art, using the description of these techniques contained in the above application, would be able to readily detect, with reasonable specificity, the extent to which the antiphosphotyrosine antibody had bound to an SBP-1/marker based peptide within the specified size range where the peptide has a phosphorylated tyrosine.

4. In this regard, in some of my experiments no peptides having phosphorylated tyrosine showed up in the selected size range (indicating kidney rejection). In others a phosphorylated tyrosine containing peptide based on SBP-1 did show up in the selected size range.

5. I am not aware of any experiments of this type where a phosphorylated tyrosine containing peptide from other than the marker protein turned up in the size range in sufficient prominence to cause a false negative problem. Of course, by overexposing beyond normal exposure times one can perceive very minor amounts of background "noise" within the size range. However, this is in such small amounts that even under overexposure conditions that noise has always been readily distinguishable from the prominence of an SBP-I based peptide within the size range that we regularly see in the case of healthy animal testing.

6. In any event, as noted in the above application, and as is evident from our laboratory's article Jose R. Torrealba et al., 5 Amer. Journal of Transplantation 58-67 (2005) (using an antibody to SBP-I rather than antiphosphotyrosine antibody), I believe that using the teachings of my application, one of ordinary skill in the art could readily develop antibodies having great specificity from the marker proteins I have identified and described the sequence of. "

As discussed supra and for the same reasons as set forth in the Office Action mailed on 08/13/2007, it is unclear why anti-phosphytyrosine antibody would only detect the SBP-1 protein or fragments in the 20-80 kD size range. Applicant's arguments and Declaration are insufficient to overcome the instant rejection for many reasons. First, the claims do not recite any steps for size cutoff filtering or antibody labeling times, so those limitations cannot be read into the claims. Further, the Examiner is not persuaded by Applicant's Declaration and argument that after size cutoff filtering only SBP-1 protein and fragments would be detected under "normal"

exposure times. The Examiner has supplied three representative evidentiary references *supra* amongst the numerous available to show a 20-80 kD protein in kidney cells having phosphorylated tyrosines that can be detected by anti-phosphotyrosine antibodies. Therefore, the Examiner is not persuaded that other proteins in the 20-80 kD range are not significantly detected by the recited method. IκB alpha is one of many proteins in that size range that are tyrosine phophorylated, ubiquitously or as a part of numerous cellular responses. Tyrosine phosphorylated SBP-1 is not specifically detected using antibodies to SBP-1 or phosphotyrosine alone. The specification does not adequately disclose a method for monitoring transplant rejection using anti-phosphotyrosine antibody or any "labeled antibody capable of binding to the marker protein in the sample or to a fragment of the marker protein in the homogenate" as encompassed by the recited method. For example, anti phosphoserine antibodies are encompassed by the instant claim recitations, though it is unclear whether anti-phosphoserine antibodies could be used to monitor kidney transplant rejection.

Further, the specification and Applicant's own publication (Torrealba et al., of record) does not support the detection of any fragments of SEQ ID NO:1 for use in the claimed invention. There is no way to detect any fragments of SEQ ID NO:1 without using antibodies that specifically bind to the specific fragment of SEQ ID NO:1. It is the Examiner's position that anti-phosphoserine antibodies will not reliably detect fragments of SEQ ID NO:1 and any arguments to the contrary are unpersuasive given the multitudes of tyrosine phosphorylated proteins within a cell at any given time that are in the range of 20-80 kD. In addition, the method in the specification and Torrealba et al. would only allow the detection of fragments between 50-

56 kD because the requisite size cutoff filtration removes proteins and peptides of less than 50 kD and the full length protein of SEQ ID NO:1 is 56kD. The Examiner is completely confused by Applicant's argument that only fragments of SEQ ID NO:1 are detectable in homogenate ("the homogenization process would fragment the marker protein (and thus the claims did cover what was regarded as the invention)" because Torrealba et al teaches on page 60, paragraph spanning left and right columns that the full-length 56 kD protein is detected in the homogenate without mention to any fragments. This reference also teaches in the same paragraph that one of ordinary skill in the art would be required to perform undue experimentation to practice the claimed invention when it teaches "We had to try numerous homogenization procedures, solubilization buffers and filtration procedures to be able to detect distinct protein spots upon blotting the membranes with anti-phosphotyrosine Ab."

Further the specification does not provide support for the use of any fragment of SEQ ID NO:1 in the claimed method. Any two or more amino acid fragment of SEQ ID NO:1 within a kidney cell could be derived from other proteins unrelated to SEQ ID NO:1 and not be any indication of the presence or absence of SBP-1 at all.

There is a lack of examples and guidance in the specification as to what antibodies can be used in the recited method of detecting phosphorylated SEQ ID NO:1 other than using antibodies that specifically bind to the protein of SEQ ID NO:1 and antibodies that specifically bind to phosphotyrosine. Therefore, one of ordinary skill in the art would be required to perform undue experimentation to practice the invention commensurate in scope with the claims.

11. Claims 2, 9 and 17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of: A method of monitoring whether an animal that has received a transplanted kidney is experiencing kidney transplant rejection, the method comprising: analyzing a sample of the kidney of the animal for the presence of a marker protein selected from the group consisting of: (a) phosphorylated protein which is SEQ:ID NO. 1 in a form comprising phosphorylated tyrosine; and (b) protein which is SEQ: ID NO. 1; wherein the analyzing comprises: contacting the sample or a homogenate thereof with **a labeled antibody that specifically binds to SEQ ID NO:1**; detecting the extent to which labeled antibody becomes bound to the marker protein or said fragment as a result thereof; and either: (i) comparing the amount of marker protein bound to the labeled antibody to a known standard to diagnose whether the animal is experiencing kidney transplant rejection, whereby the method is conducted such that if no such marker protein is thereby detected in the sample, or if the amount of marker protein thereby detected in the sample is below a known standard level, such a result would be indicative of kidney transplant rejection; or (ii) comparing the amount of said fragment bound to the labeled antibody to a known standard to diagnose whether the animal is experiencing kidney transplant rejection, whereby the method is conducted such that if no such fragment bound to the labeled antibody is thereby detected, or if the amount of such fragment

bound to the labeled antibody thereby detected is below a known standard level, such a result would be indicative of kidney transplant rejection of claim 17; wherein the animal is a primate of claim 2; and wherein the animal is a human of claim 9.

Applicant is not in possession of: a method of monitoring whether an animal that has received a transplanted kidney is experiencing kidney transplant rejection, the method comprising: analyzing a sample of the kidney of the animal for the presence of a marker protein selected from the group consisting of: (a) phosphorylated protein which is SEQ:ID NO. 1 in a form comprising phosphorylated tyrosine; and (b) protein which is SEQ: ID NO. 1; wherein the analyzing comprises: contacting the sample or a homogenate thereof with **a labeled antibody capable of binding to the marker protein in the sample, or to a fragment of the marker protein** in the homogenate; detecting the extent to which labeled antibody becomes bound to the marker protein or said fragment as a result thereof; and either: (i) comparing the amount of marker protein bound to the labeled antibody to a known standard to diagnose whether the animal is experiencing kidney transplant rejection, whereby the method is conducted such that if no such marker protein is thereby detected in the sample, or if the amount of marker protein thereby detected in the sample is below a known standard level, such a result would be indicative of kidney transplant rejection; or (ii) comparing the amount of said fragment bound to the labeled antibody to a known standard to diagnose whether the animal is experiencing kidney transplant rejection, whereby the method is conducted such that if no such fragment bound to the labeled antibody is thereby detected, or if the amount of such fragment bound to the labeled antibody thereby detected is below a known standard level, such a result would be indicative of

kidney transplant rejection of claim 17; wherein the animal is a primate of claim 2; and wherein the animal is a human of claim 9 for the same reasons as set forth in the Office Action mailed on 08/13/2007.

Applicant's arguments filed on 09/20/2007 have been fully considered, but are not found persuasive.

Applicant argues:

"It was noted by the undersigned that:

(a) the homogenation process would fragment the marker protein (and thus the claims did cover what was regarded as the invention);

(b) the antiphosphotyrosine antibody could detect the phosphorylated versions, and in any event the application taught how to make monoclonal and polyclonal antibodies which would do so as well;

(c) there was no omitted step as the claims did recite contacting, detection and evaluation steps, and in any event methods for contacting the phosphorylated versions were in the claims;

(d) the specification did enable and describe, as well, antibodies to bind to the marker protein or its fragments;

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After discussing these points examiner Haddad noted that the only remaining PTO concern related to the desire for a confirmation that the antiphosphotyrosine antibody would not be picking up unrelated fragments in such quantities that would create a high risk of false negatives. While Applicant pointed out that the monoclonal/polyclonal disclosure in the original specification would in any event resolve that concern, examiner Haddad noted that the concern could be addressed by Applicant submitting a declaration confirming that such "noise" has not been a problem given the perceived specificity under test conditions.

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2. I am very familiar with the visualization techniques, and the results thereof, as described in the above application in which homogenates of kidneys from animals were subjected to size cutoff filters, with selected size ranges being subjected to gel electrophoresis followed by immunoblotting with an antiphosphotyrosine antibody.

3. I believe that one of ordinary skill in the art, using the description of these techniques contained in the above application, would be able to readily detect, with reasonable specificity, the extent to which the antiphosphotyrosine antibody had bound to an SBP-1/marker based peptide within the specified size range where the peptide has a phosphorylated tyrosine.

4. In this regard, in some of my experiments no peptides having phosphorylated tyrosine showed up in the selected size range (indicating kidney rejection). In others a phosphorylated tyrosine containing peptide based on SBP-1 did show up in the selected size range.

5. I am not aware of any experiments of this type where a phosphorylated tyrosine containing peptide from other than the marker protein turned up in the size range in sufficient prominence to cause a false negative problem. Of course, by overexposing beyond normal exposure times one can perceive very minor amounts of background "noise" within the size range. However, this is in such small amounts that even under overexposure conditions that noise has always been readily distinguishable from the prominence of an SBP-I based peptide within the size range that we regularly see in the case of healthy animal testing.

6. In any event, as noted in the above application, and as is evident from our laboratory's article Jose R. Torrealba et al., 5 Amer. Journal of Transplantation 58-67 (2005) (using an antibody to SBP-I rather than antiphosphotyrosine antibody), I believe that using the teachings of my application, one of ordinary skill in the art could readily develop antibodies having great specificity from the marker proteins I have identified and described the sequence of. "

As discussed supra and for the same reasons as set forth in the Office Action mailed on 08/13/2007, it is unclear why anti-phosphytyrosine antibody would only detect the SBP-1 protein or fragments in the 20-80 kD size range. Applicant's arguments and Declaration are insufficient to overcome the instant rejection for many reasons. First, the claims do not recite any steps for size cutoff filtering or antibody labeling times, so those limitations cannot be read into the claims. Further, the Examiner is not persuaded by Applicant's Declaration and argument that after size cutoff filtering only SBP-1 protein and fragments would be detected under "normal" exposure times. The Examiner has supplied three representative evidentiary references *supra* amongst the numerous available to show a 20-80 kD protein in kidney cells having phosphorylated tyrosines that can be detected by anti-phosphotyrosine antibodies. Therefore, the Examiner is not persuaded that other proteins in the 20-80 kD range are not significantly detected by the recited method. IκB alpha is one of many proteins in that size range that are tyrosine phophorylated, ubiquitously or as a part of numerous cellular responses. Tyrosine phosphorylated SBP-1 is not specifically detected using antibodies to SBP-1 or phosphotyrosine alone. The specification does not adequately describe a method for monitoring transplant rejection using anti-phosphotyrosine antibody or any "labeled antibody capable of binding to the marker protein in the sample or to a fragment of the marker protein in the homogenate" as encompassed by the recited method. Applicant has disclosed only a method of monitoring whether an animal is rejecting a kidney transplant using an atnibody that specificatlly binds to SEQ ID NO:1. For example, anti phosphoserine antibodies are encompassed by the instant claim recitations, though it is unclear whether anti-phosphoserine antibodies could be used to monitor kidney transplant rejection. There is a lack of description in the specification as to what

antibodies can be used in the recited method of detecting phosphorylated SEQ ID NO:1 other than using antibodies that specifically bind to the protein of SEQ ID NO:1 and antibodies that specifically bind to phosphotyrosine and SEQ ID NO:1 using an antibody that specifically binds to SEQ ID NO:1. The specification does not adequately describe any other antibodies for use in the claimed invention.

Further, the specification and Applicant's own publication (Torrealba et al., of record) does not describe the detection of any fragments of SEQ ID NO:1 for use in the claimed invention. Any two or more amino acid fragment of SEQ ID NO:1 within a kidney cell could be derived from other proteins unrelated to SEQ ID NO:1 and not be any indication of the presence or absence of SBP-1 at all. The specification has not adequately described the genus of all fragments of SEQ ID NO:1 for use in the claimed invention.

12. No claim is allowed.

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher M. Haddad

MAHER M. HADDAD
PRIMARY EXAMINER
11/24/07

November 24, 2007

Nora M. Rooney, M.S., J.D.

Patent Examiner

TC 1600